Remarks

Claims 128-137 are pending in the subject application. By this Amendment, Applicant has canceled claim 133 and amended claim 128. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 128-132 and 134-137 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicant gratefully acknowledges the Examiner's withdrawal of the rejections under 35 U.S.C. §§ 101, 112, second paragraph, and 102(b) over Kazuguchi *et al.* and Riggs *et al.*

Claims 128-130 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention and as nonenabled by the subject specification. Applicant respectfully asserts that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that she had possession of the claimed invention and that the claims are enabled by the subject specification. Applicant respectfully submits that claims 128-130 are drawn to polypeptides comprising, or consisting of, contiguous spans of SEQ ID NO: 4 starting at position 200 and ending at position 200 of SEQ ID NO: 4 and that adequate written description of such polypeptides is provided by the subject application. However, by this Amendment, Applicant has amended claim 128 to include the limitation of claim 133. Applicant notes that claim 133 was not included under this rejection and it is respectfully submitted that this amendment should reduce issues related to the patentability of the claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 128-137 are rejected under 35 U.S.C. § 102(e) as anticipated by Greene *et al.* (U.S. Patent No. 5,786,193). In addition, claims 128-137 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under U.S.C. § 103(a) as obvious over Greene *et al.* and/or Ping-Fan (U.S. Patent No. 5,849,882). Applicant respectfully submits that the claimed invention is not anticipated by or obvious over the cited patents, regardless of whether the patents are taken alone or in combination. The Office Action indicates that the Greene *et al.* patent discloses a polypeptide that

is 100% identical to SEQ ID NO: 4 of the subject application, pointing to the polypeptide of Figure 3. Applicant respectfully traverses

It is respectfully submitted that Greene *et al.* fail to teach the claimed polypeptide fragments. For example, it is noted that the patent only appears to refer to fragments of the polypeptides of Figure 1 (SEQ ID NO: 2) or polypeptides encoded by the deposited clone ATCC 75900. As stated in from column 3, about line 50 through column 6, line 32:

> The polynucleotide of this invention was discovered in cDNA library derived from human fetal heart. It is structurally related to the polyprenyl synthetase family. It contains an open reading frame encoding a protein of 300 amino acid residues. The protein exhibits the highest degree of homology to GGPS from Neurospora crassa with 54% identity and 72% similarity over a 265 amino acid stretch. hGGPS contains both conserved aspartate motifs that denote this family of proteins, namely LLIDDEIDNSKLRRG and LGLFFQIRDDYAN (see FIG. 1). The putative active site domain of the polypeptide of the present invention is from amino acid 147 to amino 154 of SEQ ID NO:2.
>
> The polynucleotide of the present invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequence which encodes the mature polypeptide may be identical to the coding sequence shown in FIG. 1 (SEQ ID No. 1) or that of the deposited clone or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same mature polypeptide as the DNA of FIG. 1 (SEQ ID No. 1) or the deposited cDNA.
>
> The polynucleotide which encodes for the mature polypeptide of FIG. 1 (SEQ ID No. 2) or for the mature polypeptide encoded by the deposited cDNA may include: only the coding sequence for the mature polypeptide; the coding sequence for the mature polypeptide (and optionally additional coding sequence) and non-coding sequence, such as introns or non-coding sequence 5' and/or 3' of the coding sequence for the mature polypeptide.
>
> Thus, the term "polynucleotide encoding a polypeptide" encompasses a polynucleotide which includes only coding sequence for the polypeptide as well as a polynucleotide which includes additional coding and/or non-coding sequence.

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence of FIG. 1 (SEQ ID No. 2) or the polypeptide encoded by the cDNA of the deposited clone. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in FIG. 1 (SEQ ID No. 2) or the same mature polypeptide encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for a fragment, derivative or analog of the polypeptide of FIG. 1 (SEQ ID No. 2) or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

As hereinabove indicated, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in FIG. 1 (SEQ ID No. 1) or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded polypeptide.

The polynucleotides of the present invention may also have the coding sequence fused in frame to a marker sequence which allows for purification of the polypeptide of the present invention. The marker sequence may be a hexahistidine tag supplied by a pQE-9 vector to provide for purification of the mature polypeptide fused to the marker in the case of a bacterial host, or, for example, the marker sequence may be a hemagglutinin (HA) tag when a mammalian host, e.g. COS-7 cells, is used. The HA tag corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson, I., et al., Cell, 37:767 (1984)).

The term "gene" means the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons).

Fragments of the full length gene of the present invention may be used as a hybridization probe for a cDNA library to isolate the full length cDNA and to isolate other cDNAs which have a high sequence similarity to the gene or similar biological activity. Probes of this type preferably have at least 30 bases and may contain, for

example, 50 or more bases. The probe may also be used to identify a cDNA clone corresponding to a full length transcript and a genomic clone or clones that contain the complete gene including regulatory and promotor regions, exons, and introns. An example of a screen comprises isolating the coding region of the gene by using the known DNA sequence to synthesize an oligonucleotide probe. Labeled oligonucleotides having a sequence complementary to that of the gene of the present invention are used to screen a library of human cDNA, genomic DNA or mRNA to determine which members of the library the probe hybridizes to.

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 70%, preferably at least 90%, and more preferably at least 95% identity between the sequences. The present invention particularly relates to polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which either retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNAs of FIG. 1 (SEQ ID NO:1) or the deposited cDNA(s).

Alternatively, the polynucleotide may have at least 20 bases, preferably 30 bases, and more preferably at least 50 bases which hybridize to a polynucleotide of the present invention and which has an identity thereto, as hereinabove described, and which may or may not retain activity. For example, such polynucleotides may be employed as probes for the polynucleotide of SEQ ID NO:1, for example, for recovery of the polynucleotide or as a diagnostic probe or as a PCR primer.

Thus, the present invention is directed to polynucleotides having at least a 70% identity, preferably at least 90% and more preferably at least a 95% identity to a polynucleotide which encodes the polypeptide of SEQ ID NO:2 as well as fragments thereof, which fragments have at least 30 bases and preferably at least 50 bases and to polypeptides encoded by such polynucleotides.

The deposit(s) referred to herein will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for purposes of Patent Procedure. These deposits are provided merely as convenience to those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. .sctn.112. The sequence of the polynucleotides contained in the

deposited materials, as well as the amino acid sequence of the polypeptides encoded thereby, are incorporated herein by reference and are controlling in the event of any conflict with any description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted.

The present invention further relates to an hGGPS polypeptide which has the deduced amino acid sequence of FIG. 1 (SEQ ID No. 2) or which has the amino acid sequence encoded by the deposited cDNA, as well as fragments, analogs and derivatives of such polypeptide.

The terms "fragment," "derivative" and "analog" when referring to the polypeptide of FIG. 1 (SEQ ID No. 2) or that encoded by the deposited cDNA, means a polypeptide which retains essentially the same biological function or activity as such polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.

The polypeptide of the present invention may be a recombinant polypeptide, a natural polypeptide or a synthetic polypeptide, preferably a recombinant polypeptide.

The fragment, derivative or analog of the polypeptide of FIG. 1 (SEQ ID No. 2) or that encoded by the deposited cDNA may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol). Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

As indicated in these passages, the polypeptide of the invention (SEQ ID NO: 2) is encoded by the polynucleotide of SEQ ID NO: 1 and is depicted in Figure 1. The polypeptide of SEQ ID NO: 2 is not identical to the polypeptide illustrated in Figure 3 (differing at, minimally, two amino acid positions). Applicant further submits that it is clear from these passages that the '193 patent is directed to polypeptides of SEQ ID NO: 2 and fragments thereof and no discussion of polypeptide fragments of Figure 3 is discussed anywhere in the disclosure of the Greene *et al.* patent.

As shown on the attached alignment, the polypeptide of Greene *et al.* (SEQ ID NO: 2) is not identical to the polypeptide claimed herein; namely, the polypeptide of SEQ ID NO: 2 is 98.3% identical to SEQ ID NO: 4. More specifically, the polypeptide of SEQ ID NO: 4 differs from the polypeptide of Greene *et al.* by 5 polymorphic variations, located at amino acid positions 204, 205, 225, 257, and 295 of SEQ ID NO: 4. Thus, it is respectfully submitted that the Greene *et al.* patent does not anticipate the polypeptides of claim 128 as it fails to teach polypeptide fragments containing or consisting of amino acid positions 200 to 300 of SEQ ID NO: 4.

The Office Action further asserts that the claims are obvious over Greene *et al.* and/or Ping-Fan which teach a method of making enzymatically active fragments of a protein by hydrolysis of the protein. It is respectfully submitted that the combination of the prior art references fails to render the claimed invention obvious under 35 U.S.C. § 103(a). In determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification. *In re Tahorsky*, 502 F.2d 775, 780, 183 U.S.P.Q. 50, 55 (C.C.P.A. 1974).

Further, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art (*In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974)) and the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness (*In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)). It is also respectfully submitted that, in order to establish a case of *prima facie* obviousness, it is incumbent upon the Patent Office to determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the claimed species or subgenus from the disclosed prior art genus. *See, e.g., In re Ochiai*, 71 F.3d 1565, 1569-70, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); *In re Deuel*, 51 F.3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995)(A prima facie case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art); *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992; *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1991); *In re Lalu*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984) (The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.). *See also*

In re Kemps, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996) (discussing motivation to combine).

Applicant respectfully submits that hydrolysis of the protein of Greene *et al.* (SEQ ID NO: 2) would not give rise to fragments comprising the above-mentioned polymorphic variations. As a consequence, should one of skill in the art apply the method of Ping-Fan to the protein of SEQ ID NO: 2, as taught by Greene *et al.*, one would not obtain fragments comprising or consisting of amino acids 200 to 300 of SEQ ID NO: 4. Applicant further submits that one skilled in the art would have only looked to the polypeptide of SEQ ID NO: 2 in constructing such fragments given the emphasis placed on this particular sequence by the disclosure of the Greene *et al.* patent. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §§ 102(e) and (b) and 103(a) is respectfully requested.

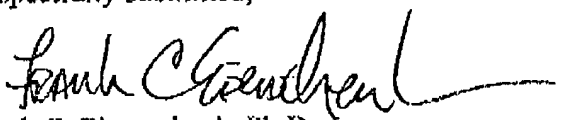
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicant expressly reserves the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicant believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/sl
Attachment: Alignment

Alignment between
* SEQ ID NO: 4 of the present application
* SEQ ID NO: 2 of Greene et al. (US patent No. 5,786,193)

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# Program:  needle
# Align_format: srspair
########################################

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# 1: SEQ ID NO: 4 of the present application
# 2: SEQ ID NO: 2 of US patent No. 5,786,193
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 300
# Identity:      295/300 (98.3%)
# Similarity:    295/300 (98.3%)
# Gaps:            2/300 ( 0.7%)
# Score: 1612.0
#
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SeqIdNo4        101 EKVLTLDHPDAVKLFTRQLLELHQGQGLDIYWRDNYTCPTEEEYKAMVLQ 150
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